REMARKS

Reconsideration of this application, as amended, is respectfully requested.

Claims 1-16 were originally pending in the application. Claims 15 and 16 were cancelled without prejudice or disclaimer and new claims 17 and 18 were added. Claims 1-4, 10, and 11 were amended to correct for form and to further clarify the Applicant's invention. A copy of the claims with the amendments shown are attached as Appendix A. Claims 1-14, 17, and 18 are now pending.

Support for the amendments and new claims can be found in the application as originally filed. For example, Claim 1 was amended to remove the use of the parenthetical form; the added subject matter in Claim 2 can be found in the application on page 15, line 29 and page 16, lines 7 and 8; the amendments to claims 3 and 4 was to correct for grammar; the amendment of Claim 10 can be found in the application on page 8, lines 2-4; and the subject matter of Claim 11 can be found in original Claim 10. The subject matter of new Claim 17 can be found in original Claim 10 and 11 as well as on page 18, lines 8-18, in the application. The subject matter of new Claim 18 can be found in the application on page 18, lines 14-16. Accordingly, no new matter has been introduced into the application as a result of the above amendments. Applicant respectfully submits that the claims, as amended, are in condition for an allowance.

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TELEPHONE (312) 715-1000

1. Rejection of claims 1-15 under 35 U.S.C. 112, second paragraph.

Claims 1-15 stand rejected for alleged indefiniteness. Specifically, the Examiner contends that Claim 1 is unclear in its use of the parenthetical expression (type I). Furthermore, the Examiner contends that the recitation of "combinations of the foregoing" renders Claim 10 indefinite. Claim 1, however, has been amended to remove the use of the parenthetical. Furthermore, the aforementioned recitation in Claim 10 was deleted by amendment. In view of the foregoing amendments, the Applicant respectfully submits that the § 112, second paragraph, rejection no longer applies and urges the Examiner to withdraw it.

2. Rejection of claims 1-16 under 35 U.S.C. 112, first paragraph.

Claims 1-16 stand rejected for alleged lack of enablement. The specification was also objected to for the same reason. The Examiner contends that the claimed use of anti-VLA4 antibodies for therapeutic use is not supported by the specification. Applicants respectfully traverse this rejection. In making the rejection, the Examiner has raised a number of enablement issues which include the timing of treatment, duration of treatment, the relevancy of NOD model results to human diabetes, and use of antibody fragments as therapeutic agents. These issues are addressed below in the order of their presentation in the Action.

The Examiner contends that the subject matter of Claim 8, drawn to a method for preventing insulin dependent diabetes, is not enabled as the specification allegedly provides no guidance for

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determining the appropriate time "prior" to development of overt diabetes when the antibodies are to be administered or the duration of the treatment. The Applicant respectfully disagrees.

The Applicant's invention, as presently claimed, relates to a method for the prevention of insulin dependent (type I) diabetes by administering anti VLA4 antibodies or fragments thereof and other agents, e.g., soluble proteins, which are capable of binding to VLA4, an integrin found on the surface of lymphocytes and macrophages. See the application on page 8, lines 1-8 and page 18, lines 8-21. The Applicant surprisingly discovered that by administering a VLA4 binding agent (e.g., an anti-VLA4 antibody R1-2) in a subject predisposed to diabetes (e.g., an adoptive transfer model) the incidence of overt type I diabetes development was significantly reduced. The NOD mouse model, an art recognized model for human type-I diabetes, was used to demonstrate the utility of Applicant's claimed invention. See the application on page 19, lines 29-33.

The Applicant's specification, as originally filed, adequately describes how to make and use the Applicant's invention and thus fully complies with the requirements of 35 U.S.C. § 112, first paragraph. As taught by the application, the development of type I diabetes is divided conceptually into six stages beginning with genetic susceptibility (stage I) and ending with complete β cell destruction (stage VI). See page 1, lines 21-24. By administering VLA4 binding agent composition to a prediabetic subject at a stage prior to the development of overt diabetes as measured by a serum

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glucose level of less than 250 mg/dL (Claim 8), it is possible to halt further loss of insulin-producing β cell as it has been established that prediabetic events precede the development of overt diabetes by a prolonged period of time. See the application on page 4, lines 29-32. The specification describes a number of known markers which may be used to identify prediabetic subjects and to estimate the rate of disease onset in such subjects. These markers include genetic suspectibility markers (HLA typing), immunological markers (detection of islet and insulin autoantibodies) and metabolic markers (first phase insulin secretion to intravenous glucose preceding the development of hyperglycemia). See the application on page 6, lines 13-27. By identifying these risk factors in a subject, it is possible to determine the various stages prior to disease onset.

With respect to the duration of treatment, the Applicant teaches that anti-VLA4 mAb, e.g., R1-2 mAb, prevented diabetes onset during treatment. Furthermore, the residual beneficial results of treatment were extended as long as two months following the last R1-2 injection as determined by consistent normoglygemic plasma glucose values in the experimental subjects. See, Figure 3 and page 27, lines 3-24, in the application. The results shown in Figure 3 imply that while some residual protective benefit occurs even after cessation of mAb treatment for two months, continued treatment with anti-VLA antibodies is generally required in order to sustain the full protective effect. The exact duration of therapeutic treatment with VLA4 binding agents (e.g. mAbs), like

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any other treatment, is dependent on a patient-to-patient basis. See page 30, lines 13-29, in the application.

The Examiner further argues that the specification does not show how a two week post transfer treatment in NOD mice translates to treatment in humans. Applicant respectfully disagrees.

As discussed on page 19, line 25 to page 20, line 22, in the specification, the adoptive transfer model of diabetes using spontaneously diabetic non-obese (NOD) mice is a particularly useful model for determining the efficacy of anti-VLA4 antibodies in a method of treating type I diabetes. As taught in the specification, NOD mice are an art recognized animal model for human type I diabetes. See page 7, lines 9-11; page 19, line 25 to page 20, line 22. See, for example, Castano and Eisenbarth (1990, Annu. Rev. Immunology, Vol. 8: 647-79), Miller et al. (1988, J. Immunol., Vol. 140: 52-58), and Hutchings et al. (1990, Nature, Vol. 348: 639-642). (Copies of these references are attached). For instance, NOD mice and humans both show (a) a strong genetic association of diabetes with loci of the major histocompatibility complex; and (b) an autoimmune pathogenesis evidenced by insulitis, anti-islet cell antibodies, and modulating effects of cyclosporin A. See the application at 20, lines 1-22. Because of these similarities, the art has recognized NOD mice as an important model for human type I diabetes.

The specification also provides adequate guidance with respect to treatment of prediabetic subjects with VLA4 binding agents. For instance, the specification teaches suitable dosage ranges (page

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18, line 27 to page 19, line 22)); administration regimen (page 18, line 30); mode of administration as well as suitable pharmaceutical carriers (page 18, lines 19-26). Accordingly, the specification adequately demonstrates the operability and utility of the claimed method and further provides guidance with respect to administration of the VLA4 binding agents to prediabetic subjects.

The Examiner also alleges that the subject matter of claims 10-16, drawn to a method for preventing insulin dependent diabetes by administering "fragments of antibodies," is unsupported by the specification as there is no indication in the specification that binding peptides specific for VLA4 have any effect on any form of diabetes other than Type I diabetes. Furthermore, the Examiner argues that the specification provides no guidance with respect to the identity of various antibody fragments or binding peptides or molecules which can be used in the claimed invention nor is there guidance in determining the effective amount to prevent onset of diabetes. The Applicant respectfully disagrees.

With respect to antibody fragments, the specification teaches that fragments of antibodies which are useful in the presently claimed invention are those which, like whole anti-VLA4 antibodies, are capable of binding to VLA4 antigen. Suitable types of antibody fragments include Fab, Fab', $F(ab')_2$, and F(v) fragments. See the application on page 13, lines 20-22. Furthermore, the effective amounts of VLA4 binding agents, such as anti-VLA4 antibody fragments, for use in the claimed method are described on page 13, line 27 to page 19, line 22 in the specification. Finally, several

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VLA4 binding peptides are listed on page 18, lines 8-18, in the specification. These examples include soluble VCAM, fibronectrin and their derivatives. Thus contrary to the Examiner, the specification does provide guidance as to the identity of antibody fragments, and the types of binding peptides which can be used in the claimed invention. There is no reason for the Examiner to question the validity of the Applicant's asserted utility regarding antibody fragments in the absence of any information proving otherwise.

Regarding to the remaining issues relating to the type of diabetes being treated and the concentration recited in Claim 15, the Applicant respectfully draws the Examiner's attention to the aforementioned amendments to claims 1 and 10 which recite "insulin dependent type I diabetes." Claim 15, however, has been cancelled and thus the rejection no longer applies.

In light of the above discussion, the Applicant respectfully submits that the claims and specification are fully enabled. The specification adequately describes how to make and use the invention and thus satisfies the requirements of 35 U.S.C. § 112, first paragraph. Withdrawal of the § 112 rejection is in order and is respectfully urged.

3. Rejection of claims 1-16 under 35 U.S. 101.

Claims 1-16 stand rejected for alleged lack of utility. The Examiner contends that data taken from a transfer NOD mouse model cannot be extrapolated to predict human efficacy in vivo.

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Furthermore, the Examiner contends that therapeutic use of antibodies in human therapy is dubious in view of teachings by Waldmann (1991) Science, Vol. 252, pp. 1657-1662) and Harris et al. ((1993) TIBTECH, Vol. 11, pp. 42-45). Applicant respectfully traverses this rejection.

The Examiner has raised several objections to the proof of utility provided by the instant specification. Each of these objections will be addressed below. As a threshold matter, however, Applicants note that generally, when a claim is directed to treatment of diseases, patentable utility can be supported by either animal studies or by in vitro studies for which a correlation between study and disease can be shown. Ex parte Powers, 220 U.S.P.Q. 924,925 (B.P.A.I. 1982). Furthermore, with respect to the Applicant's asserted utility of an invention, MPEP 608.01(p) supports: "If the asserted utility of a compound is believable on its face to persons skilled in the art in view of the contemporary knowledge in the art, then the burden is on the examiner to give adequate support for rejections for lack of utility under this section [i.e., § 101] (*In re Gazave*, 54 CCPA 1524, 154 USPQ 92)." For the reasons discussed below, Applicants respectfully submit that the animal studies used in the present invention adequately support patentable utility of the instant claimed invention.

The Examiner's first objection is that results taken from the transfer disease model are insufficient to establish therapeutic utility or human efficacy in vivo. The Applicant respectfully, but

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forceably, disagrees. The demonstrated prevention of diabetes onset with VLA4 binding agents in an art recognized disease transfer animal model, as shown in Examples 1 and 2 of the instant specification, provides adequate support for the operativeness of the claimed invention.

Example 1 demonstrates that pre-treatment of diabetogenic splenocytes from NOD mice with anti-VLA4 antibodies prior to transfer into recipient mice followed by further treatment of the recipient mice for day 12 or 24 post-transfer conferred a protective effect against the development of diabetes. For instance, Figure 1 shows that after day 12 post-treatment with anti-VLA4 antibody R1-2 or nonspecific binding antibody IgG2b, 56 to 60% of subjects receiving IgG2b relative to only 12.5 % (1/8) of the anti-VLA4 antibody-treated subject became diabetic by day 29. Further confirmation of this result is shown in Figure 2 where after day 24 post-treatment with R1-2 or IgG2b, 100% of subjects receiving IgG2b antibody became diabetic while only 20% of R1-2 treated recipients developed diabetes. See generally the application at page 24, line 23, to page 25, line 16.

Example 2 also shows that administration of anti-VLA4 antibodies delays progression of insulitis in the acute transfer model of the disease. For instance, recipient mice treated through day 14 post-transfer developed only 24% grade II-IV insulitis while those treated with IgG2b developed 74% severe insulitis. The results taken from the acute transfer model of diabetes indicate that administration of a VLA4 binding agent, e.g., anti-VLA4

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antibodies, causes a significant reduction of both diabetes onset and insulitis upon adoptive transfer of diabetogenic spleen cells.

In addition, the Applicant respectfully draws the Examiner's attention to the attached Declaration of Linda C. Burkly which is submitted in further support of the patentability of the claimed invention. Dr. Burkly's Declaration includes two additional experiments (Examples 3 and 4) which demonstrate the utility of the invention in an art-recognized animal model for human type I diabetes. In Example 3, R1-2 mAb was evaluated in a spontaneous disease model which employs NOD mice. Both untreated NOD mice and NOD mice treated with an irrelevant antibody IgG2b were used as controls. Exhibit A figure summarizes the results and shows that R1-2 administration produced a marked delay in diabetes onset. In contrast, the two control groups developed diabetes as early as 13 weeks. Dr. Burkly found that the results taken from the spontaneous disease model parallel those obtained from the adoptive transfer model (See, for instance, Figures 1 and 2 in the application).

Example 4 in Dr. Burkly's Declaration is an adoptive transfer experiment which compares the efficacy of two different anti-VLA4 antibodies, R1-2 and PS/2, and an irrelevant antibody IgG2b in the claimed method. Recipient mice receiving NOD donor cells, non-NOD donor cells and no cells served as controls. Table 1 (attached as Exhibit B) summarizes the results and shows that both R1-2 and PS/2 were equally effective in inhibiting development of overt diabetes during four weeks post-transfer. In contrast, 84% of the total

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recipients receiving NOD splenocytes with or without IgG2b antibody treatment developed diabetes between 2-3 weeks post-transfer. Thus, Example 4 also shows that anti-VLA4 antibodies are useful in inhibiting diabetes onset.

Furthermore, the Applicant respectfully draws the Examiner's attention to a recent publication (Yang et al. Proc. Natl. Acad. Sci. USA, Vol. 90, pp 10494-10498 (November 1993), copy attached) which relates to the use of anti-VLA4 antibodies in inhibiting insulitis and preventing diabetes in NOD mice. As the Examiner will note, this reference was published subsequent to the Applicant's U.S. filing date of February 9, 1993 and thus cannot be applied as a reference against the present claims. According to Yang, R1-2 was found to effectively inhibit insulitis (Table 1 in Yang at page 10495) and prevent diabetes (Table 2 in Yang at page 10496) in NOD mice. In summary, the Yang et al. reference independently confirms the Applicant's discovery regarding the utility of anti-VLA4 antibodies in inhibiting insulitis and preventing diabetes.

The Examiner's second objection is that the anti-VLA4 antibodies are not useful for therapeutic applications based on Waldmann's and Harris' teachings. The Applicant submits that the Examiner's reliance on Waldmann and Harris is misplaced.

The Waldmann article relates to a review of the use of monoclonal antibodies in diagnosis and therapy. However, the Waldmann reference does not change Applicant's showing in any way. Although Waldmann does point out certain difficulties that have

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arisen in the development of monoclonal antibody therapies, Waldmann points out numerous successful applications of such approaches ("Monoclonal antibodies have been applied clinically to the diagnosis and therapy of an array of human disorders ..."). See Waldmann at 1657, left column, abstract and paragraph 2. For example, Waldmann points out successful applications of monoclonal antibody approaches for allograft rejection, β cell lymphomas and rheumatoid or psoriatic arthritis. See, for instance, Waldmann at page 1657, left column, paragraph 2, and right column, paragraph 2; page 1658, left column, paragraph 2 and right column, paragraph 1. Accordingly, Applicant respectfully submits that Waldmann's teachings concerning successful use of antibodies as therapeutic agents do not lend support to the Examiner's allegation concerning lack of utility.

The Harris article is similar to Waldmann in that it merely indicates that there are problems in using pure murine antibodies for in vivo human therapy. However, the Harris article specifically notes that "researchers [have] great confidence that the newer technologies generating more humanized antibodies will lead to the availability of effective therapeutics." See Harris at page 42, column 3. Since the present invention expressly teaches the use of antibodies other than pure murine antibodies, the Examiner's reliance on Harris is misplaced. See the application on page 16, line 9-33 and page 17, lines 1-28.

The Applicant submits that the Examiner's reliance on the Harris and Waldmann articles is also misplaced in view of

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references demonstrating the therapeutic use of monoclonal antibodies in humans. See, attached references. Contrary to the Examiner's position regarding the utility of murine and other types of antibodies, the attached references show that Muromonab™ CD-3, an FDA approved commercial murine monoclonal antibody (mAb OKT3), is efficacious for the in vivo treatment of human kidney graft rejection (Hooks et al., Pharmacotherapy, Vol. 11(1), pages 26-37 (1991)). Furthermore, human clinical trials with murine/human chimeric mAbs to CD4 (Knox et al., Blood, Vol. 77(1), page 20-30 (1991)) and CD7 (Kirkham et al., J. Rheum., Vol. 19(9), page 1348-1352 (1992)) demonstrate their safety and efficacy of mAbs as human therapeutic agents in the treatment of mycosis fungoides and rheumatoid arthritis, respectively. More recently, a chimeric anti-CD4 mAb (cM-T412) was shown to be safe and beneficial for treating refractory rheumatoid arthritis in a preliminary human clinical trial (Moreland et al., Arthritis and Rheumatism, Vol. 36(3), (March 1993)). Accordingly, the Applicant respectfully submits that the Examiner's reliance on Waldmann and Harris is misplaced and urges the Examiner to withdraw the § 101 rejection.

4. Rejection of Claim 16 under 35 U.S.C. 102(b) in view of Issekutz et al.

Claim 16 stands rejected as being anticipated in Issekutz et al. ((1991) J. Immunol., Vol. 147, pp. 4178-4184. This rejection, however, no longer applies in view of the cancellation of this claim by the present amendment.

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CONCLUSION

In view of the above discussion, amendment and Dr. Burkly's Declaration, the Applicant respectfully submits that Claims 1-14, 17 and 18 are in condition for an allowance and urges the Examiner to issue a Notice to this effect. If the Examiner believes that any discussion of this communication would be helpful, he/she is invited to contact the undersigned at 312/715-1000.

Respectfully submitted,
ALLEGRETTI & WITCOFF, LTD.

Dated: Feb. 3, 1994

By: _____
Emily Miao
Reg. No. 35,285

Enclosures:

(1) References:
- (a) Yang et al., Proc. Nat'l. Acad. Sci. USA, Vol. 90, pages 10494-10498 (1993)
- (b) Hooks et al., Pharmacotherapy, Vol. 11(1), pages 26-37 (1991)
- (c) Knox et al., Blood, Vol. 77(1), page 20-30 (1991)
- (d) Kirkham et al., J. Rheum., Vol. 19(9), page 1348-1352 (1992)
- (e) Moreland et al., Arthritis and Rheumatism, Vol. 36(3), (March 1993)
- (f) Castano et al. (1990, Annu. Rev. Immunology, Vol. 8: 647-79)
- (g) Miller et al. (1988, J. Immunol., Vol. 140: 52-58)
- (h) Hutchings et al. (1990, Nature, Vol. 348: 639-642)

(2) Declaration of Linda C. Burkly with Exhibits A and B

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10 SOUTH WACKER DRIVE
CHICAGO, ILLINOIS 60606
TELEPHONE (312) 715-1000